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L2: Entry 69 of 76 File: USPT Apr 6, 1982

DOCUMENT-IDENTIFIER: US 4323563 A
TITLE: Fat emulsion for intravenous injection

Abstract Text (1):
A pharmaceutically acceptable emulsifier for preparing fat emulsions for intravenous injection comprising purified phospholipid of vegetable origin, containing less than 5% of glycolipid, and having a degree of hydrogenation of 30-50 as defined by the iodine number is prepared from vegetable phospholipid by a three-step procedure comprising (in any order) (1) isolation of a fraction containing phosphatidylcholine, (2) partial hydrogenation to produce the desired iodine value, and (3) removal of glycolipid.

Detailed Description Text (15):
Phospholipid solution after removal of glycolipid should be submitted to aseptic filtration, such as filtration through a Millipore.RTM. filter, and then can be used as an emulsifier for the fat emulsion for intravenous injection.

Detailed Description Text (61):
It will be seen from Tables 5 and 6 that fat emulsion using soybean phospholipid from which glycolipid was removed after hydrogenation is desirable as a fat emulsion for intravenous injection.

Detailed Description Text (70):
The fat emulsion used for test group 1 in Example 8 was used to test acute toxicity in SD strain male rats, weighing ca. 200 g. The LD.sub.50 value obtained was 142 ml/kg body weight. Subacute toxicity test was carried out by 30 continuous administrations of 20 or 40 ml/kg body weight, but none of the rats died. Their body weight increased at the same rate as that of rats give physiological saline solution, and there was no evidence of anemia. The fat emulsion obtained by this invention was thus found to be fully safe.

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L5: Entry 6 of 15 File: USPT Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6139871 A
** See image for Certificate of Correction **
TITLE: Liposome compositions and methods for the treatment of atherosclerosis

Brief Summary Text (14):
Paradoxically, intravenous infusion of phospholipids and liposomes has been shown to produce regression of atherosclerotic plaques although serum lipid levels are transiently elevated. Williams et al., Perspect. Biol. Med., 27:417-431 (1984). In some instances, however, cholesterol associated with development and progression of atherosclerosis may increase following liposome administration.

Brief Summary Text (19):
Also provided are methods for treating atherosclerosis employing the pharmaceutical compositions of the present invention. The compositions are administered to animals having atherosclerosis. Often, the compositions will be serially administered over a period of time. Generally, the compositions will be administered parenterally, usually intravenously. The methods may be employed therapeutically or prophylactically. The methods of the present invention are also useful for treatment of hypoalphalipoproteinemia and hyperlipidemias.

Detailed Description Text (27):
The liposomes may be administered in many ways. These include parenteral routes of administration, such as intravenous, intramuscular, subcutaneous, and intraarterial. Generally, the liposomes will be administered intravenously. Often, the liposomes will be administered into a large central vein, such as the superior vena cava or inferior vena cava, to allow highly concentrated solutions to be administered into large volume and flow vessels. The liposomes may be administered intraarterially following vascular procedures to deliver a high concentration directly to an affected vessel. The liposomes may also be administered directly to vessels in a topical manner by surgeons during open procedures. In some instances, the liposomes may be administered orally or transdermally. The liposomes may also be incorporated in vascular stents for long duration release following placement. This is particularly effective for angioplasty treatment of restenosis of lesions in the coronary arteries.

Detailed Description Text (28):
As described above, the liposomes will generally be administered intravenously in the methods of the present invention. Often multiple treatments will be given to the patient, generally weekly. Typically, the therapy will continue for about 4-16 weeks (4-16 treatments), usually about 10 weeks (10 treatments). The duration and schedule of treatments may be varied by methods well known to those of skill.

Detailed Description Text (82):
The ability of the animals to tolerate and remove repeated injections of phospholipid and the consequences of administering excess phospholipid on plasma lipid levels were examined. Chronic short term (one week) administration of Intralipid, an emulsion of triglycerides and phospholipids, causes increased LDL levels. Although the phospholipid content of Intralipid is comparable to the dose of 300 mg/kg LUV.sub.100 per injection of the present treatment regimen, Intralipid is generally given intravenously on a daily basis as a nutritional supplement.

Other Reference Publication (4):
Adams, et al., "Modification of aortic atheroma and fatty liver in cholesterol-fed rabbits by intravenous injection of saturated and polyunsaturated lecithins," J. Pathol Bacteriol 94:777-87 (1967).

Other Reference Publication (7):
Aviram, et al., "Macrophage cholesterol removal by triglyceride-phospholipid emulsions," Biochem Biophys Res Commun 155:709-713 (1988).

Other Reference Publication (20):
Ellens, et al. "In vivo fate of large unilamellar sphigomyelin-cholesterol liposomes after intraperitoneal and intravenous injection into rats," Biochem Biophys Acta 674:10-18 (1981).

Other Reference Publication (29):
Howard, et al., "Atherosclerosis induced in hypercholesterolemic baboons by immunological injury; and the effects of intravenous polyunsaturated phosphatidyl choline," Atherosclerosis 14;17-29 (1971).

Other Reference Publication (52):
Senior, et al., "Tissue districution of liposomes exhibiting long half-lives in the circulation after intravenous injection," Biochim. Biophys. Acta 839:1-8 (1985).

Other Reference Publication (55):
Stafford, W.W. et al., "Regression of atherosclerosis affected by intravenous phospholipid," Artery 1:106-114 (1975).

Other Reference Publication (59):
Thompson, et al., "Effects of intravenous phospholipid on low density lipoprotein turnover in man," Eur J Clin Invest 6:241-248 (1976).

Other Reference Publication (62):
Williams et al., "Intravenously Administered Lecithin Liposomes: A Synthetic Antiaatherogenic Lipid Particle," Perspect. Bio. Med. 27:417-431 (1984).

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L7: Entry 43 of 74 File: USPT Sep 9, 1997

DOCUMENT-IDENTIFIER: US 5665382 A
TITLE: Methods for the preparation of pharmaceutically active agents for in vivo delivery

Detailed Description Text (59):
Modifications of the hemoglobin molecule or its conformation may be associated with changes in oxygen binding affinity. For example, association with 2,3-diphospho-glycerate (2,3-DPG, as occurs within the RBC) loosens the association between oxygen and hemoglobin, facilitating release of oxygen to tissues; serum levels of 2,3 DPG rise under physiologic conditions in which an increased delivery of oxygen is desirable, for example, at high altitudes and during pregnancy. Oxidation of the iron ion in the heme prosthetic group from Fe(II) to Fe(III) results in the formation of methemoglobin (met-Hb), which binds water so tightly as to preclude oxygen transfer. This oxidation or `auto-oxidation` is an ongoing process in vivo which is maintained in check by a system of redox enzymes within the red blood cell.

Detailed Description Text (112):
Water-soluble drugs may also be encapsulated within the IHC shell by a method of double emulsion. First, an aqueous drug solution is emulsified with a biocompatible oil to obtain a water-in-oil (W/O) emulsion. The W/O emulsion is treated as an oil phase and subjected to ultrasonic irradiation with an aqueous hemoglobin solution as above to produce IHC containing within their shell, a microemulsion of the desired water-soluble drug. Emulsifiers contemplated for use in this embodiment of the present invention include the Pluronics (block copolymers of polyethylene oxide and polypropylene oxide), phospholipids of egg yolk origin (e.g., egg phosphatides, egg yolk lecithin, and the like); fatty acid esters (e.g., glycerol mono- and di-stearate, glycerol mono- and di- palmitate, and the like). Water-soluble drugs contemplated for use in this embodiment of the present invention include antineoplastic drugs such as actinomycin, bleomycin, cyclophosphamide, duanorubicin, doxorubicin, epirubicin, fluorouracil, carboplatin, cisplatin, interferons, interleukins, methotrexate, mitomycins, tamoxifen, estrogens, progestogens, and the like.

Detailed Description Text (114):
In order to make the IHC in a greater likeness to red blood cells, a phospholipid bilayer can be formed around the crosslinked hemoglobin microbubbles. Such a bilayer results in the formation of a true `red cell analog` and may be created in a two step process. Charged phospholipids or lipids utilized in the formation of this bilayer include phosphatidyl choline, phosphatidyl ethanol amine, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, sphingomyelin, dimyristoylphosphatidic acid, dipalmitoyl phosphatidic acid, sarcosinates (sarcosinamides), betaines, monomeric and dimeric alkyds, and the like. Nonionic lipids may also be utilized in this invention, including polyethylene fatty acid esters, polyethylene fatty acid ethers, diethanolamides, long chain acyl hexosamides, long chain acyl amino acid amides, long chain amino acid amines, polyoxyethylene sorbitan esters, polyoxy glycerol mono- and di-esters, glycerol mono- and di-stearate, glycerol mono- and di-oleate, glycerol mono- and di-palmitate, and the like.

Detailed Description Text (115):
Another variation on this technique is to utilize photopolymerizable lipids or lipids that may be readily crosslinked via a chemical reaction in order to provide a more stable lipid `membrane ` coat. Photopolymerizable lipids that may be utilized in the present invention include acrylate or methacrylate substituted lipids (such as phosphatidyl choline, phosphatidyl ethanol amine, phosphatidyl serine, phosphatidyl glycerol, dimyristoylphosphatidic acid, dipalmitoyl phosphatidic acid, and the like); lipids with native polymerizable unsaturation (such as unsaturated phosphatidyl cholines with diacetylene groups or conjugated diene groups, and the like), and so on. Lipids that readily undergo crosslinking via thiol-disulfide exchange also are good candidates for the formation of a stable lipid coat for the IHC. Examples of such lipids include derivatives of phosphatidyl cholines esterified with lipoic acid, and the like.

Detailed Description Text (184):
Biocompatible liquids contemplated for use in this embodiment are the same as those described above. In addition, parenteral nutritional agents such as Intralipid (trade name for a commercially available fat emulsion used as a parenteral nutrition agent; available from Kabi Vitrum, Inc., Clayton, N.C.), Nutralipid (trade name for a commercially available fat emulsion used as a parenteral nutrition agent; available from McGaw, Irvine, Calif.), Liposyn III (trade name for a commercially available fat emulsion used as a parenteral nutrition agent (containing 20% soybean oil, 1.2% egg phosphatides and 2.5% glycerin); available from Abbott Laboratories, North Chicago, Ill.), and the like may be used as the carrier of the drug particles. Alternatively, if the biocompatible liquid contains a drug-solubilizing material such as soybean oil (e.g., as in the case of Intralipid), the drug may be partially or completely solubilized within the carrier liquid, aiding its delivery. An example of such a case is the delivery of taxol in Intralipid as the carrier. Presently preferred biocompatible liquids for use in this embodiment are parenteral nutrition agents, such as those described above.

Detailed Description Text (219):
Five ml of a commercially available fat emulsion (Intralipid, an aqueous parenteral nutrition agent--containing 20% soybean oil, 1.2% egg yolk phospholipids, and 2.25% glycerin) was used as a control. The control utilizes egg phosphatide as an emulsifier to stabilize the emulsion. A comparison of serum levels of the triglycerides in the two cases would give a direct comparison of the bioavailability of the oil as a function of time. In addition to the suspension of polymeric shells containing 20% oil, five ml of a sample of oil-containing polymeric shells in saline at a final concentration of 30% oil was also injected. Two rats were used in each of the three groups. The blood levels of triglycerides in each case are tabulated in Table 3, given in units of mg/dl.

Detailed Description Text (222):
Such a system of soybean oil-containing polymeric shells could be suspended in an aqueous solution of amino acids, essential electrolytes, vitamins, and sugars to form a total parenteral nutrition (TPN) agent. Such a TPN cannot be formulated from currently available fat emulsions (e.g., Intralipid) due to the instability of the emulsion in the presence of electrolytes.

Detailed Description Text (240):
Cyclosporine is currently delivered in oral form either as capsules containing a solution of cyclosporine in alcohol, and oils such as corn oil, polyoxyethylated glycerides and the like, or as a solution in olive oil, polyoxyethylated glycerides, and the like. It is also administered by intravenous injection, in which case it is dissolved in a solution of ethanol (approximately 30%) and Cremaphor (polyoxyethylated castor oil) which must be diluted 1:20 to 1:100 in normal saline or 5% dextrose prior to injection. Compared to an intravenous (i.v.) infusion, the absolute bioavailibility of the oral solution is approximately 30% (Sandoz Pharmaceutical Corporation, Publication SDI-Z10 (A4), 1990). In general,

the i.v. delivery of cyclosporine suffers from similar problems as the currently practiced i.v. delivery of taxol, i.e., anaphylactic and allergic reactions believed to be due to the Cremaphor, the delivery vehicle employed for the i.v. formulation. In addition, the intravenous delivery of drug (e.g., cyclosporike) encapsulated as described here avoids dangerous peak blood levels immediately following administration of drug. For example, a comparison of currently available formulations for cyclosporine with the above-described encapsulated form of cyclosporine showed a five-fold decrease in peak blood levels of cyclosporine immediately following injection.

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